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Editorial

Finding a Workable Balance

Regulation of Genetic Testing in the Human Genome Era

The Human Genome Project (HGP) will provide us with an unprecedented view into our biological constitutions. The genetic knowledge gained through the efforts of the HGP is expected to facilitate diagnosis and management of disease, guide development and use of pharmacological agents, and offer the ability to predict disease susceptibility. In the midst of this revolution, we are faced not only with the chance to capitalize on the benefits of new genetic knowledge, but also with the challenge of protecting individuals from potential adverse ethical, legal, and social consequences due to their genetic identity. Realizing the need to achieve a balance between these benefits and risks, from its inception the HGP established the National Institutes of Health-Department of Energy (NIH-DOE) Joint Working Group on the Ethical, Legal, and Social Implications of Human Genome Research (ELSI Working Group). In early 1995, ELSI convened the Task Force on Genetic Testing, charging it with reviewing genetic testing in the United States and making recommendations to ensure the development of safe and effective genetic tests. In its final report, published in September 1997 (http://www.nhgri.nih.gov/ELSI/TFGT_final/), the Task Force concluded that, on the whole, genetic testing was developing successfully in the United States. However, the Task Force identified several concerns about genetic testing, including i) how genetic tests are introduced into clinical practice; ii) the adequacy and appropriate regulation of laboratory quality assurance; iii) the understanding of genetics by health care providers and patients; and iv) the continued availability and quality of testing for rare diseases. The Task Force, along with the ELSI Working Group, also recommended the establishment of an advisory panel for genetic testing. In response, the Secretary of the Department of Health and Human Services (DHHS) chartered, in June 1998, the Secretary's Advisory Committee on Genetic Testing (SACGT) to help the DHHS formulate policies on the development, validation, and regulation of genetic tests.

To address appropriate coordination of genetic testing activities and policies, the SACGT was designed to include overlapping membership with the Clinical Laboratory Improvement Advisory Committee (CLIAC) of the Centers for Disease Control and Prevention (CDC) and the Medical Devices Advisory Committee of the Food and Drug Administration (FDA). In addition to members from CLIAC and FDA, the SACGT was formulated to have diverse representation from academic and private sectors, including physicians, doctoral scientists, bioethicists, lawyers, and genetic counselors. The SACGT established and maintains a website to keep the public informed of its charter and activities (http://www4.od.nih.gov/oba/sacgt.htm). At the first meeting of the SACGT in June 1999, Assistant Secretary for Health and Surgeon General Dr. David Satcher asked the Committee to assess, in consultation with the public, the adequacy of current oversight of genetic tests. As a first step, the SACGT convened in October 1999 and held 2 days of meetings in which public and expert testimony was heard to provide a synopsis of current oversight of genetic testing and ethical issues. Subsequently, the SACGT moved to gather broader public input through a process that involved a Federal Register notice published on December 1, 1999, a targeted mailing to 2500 individuals and organizations, a public consultation meeting on January 27, 2000, and a review of the literature on oversight. To guide public comment, the SACGT compiled and published on its website a document titled "A Public Consultation on Oversight of Genetic Tests," which provided background information on genetic testing, current oversight mechanisms, and summary recommendations of the NIH-DOE Task Force on Genetic Testing. In the document, the SACGT posed the following five questions for comment:

1. What criteria should be used to assess the benefits and risks of genetic tests?
2. How can the criteria for assessing the benefits and risks of genetic tests be used to differentiate categories of tests? What are the categories and what kind of mechanism could be used to assign tests to different categories?
3. What process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category?
4. What are the options for oversight of genetic tests and the advantages and disadvantages of each option?
5. What is the appropriate level of oversight for each category of genetic test?

The Clinical Practice Committee of the Association for Molecular Pathology (AMP), in consultation with the Executive Committee of AMP, submitted a written response to the five questions. The AMP response, which can be viewed in its entirety at http://www.ampweb.org/secadvise.htm, expressed the belief that genetic testing is a medical service with potential benefits and risks to which the highest standards of laboratory quality assurance and confidentiality must be applied, and stressed that genetic testing should occur in the context of an informed dialogue between patient and physician.

Further highlighted was the AMP's view that the role of individual genetic tests should be defined in the context of practice guidelines for the diagnosis and management of specific medical conditions. With regard to regulatory oversight of genetic testing, AMP advocated continuing to build on guidelines enunciated in the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) and those of the College of American Pathologists and American College of Medical Genetics. On February 24–25, 2000, the SACGT met and reviewed public input. Critical issues raised by the public included concerns about potential discrimination based on genetic test results and ensuring the quality of, and access to, genetic testing.

The SACGT recently released its preliminary draft recommendations for oversight of genetic testing (http://www4.od.nih.gov/oba/sacgt3–00final.pdf). Key features of the draft include the recommendation that additional oversight is warranted for all genetic tests. In a significant departure from current oversight, the draft recommends that "the FDA should be involved in the review of all new genetic tests but the review should be appropriate to the level of complexity of the information generated by the test. The FDA should develop flexible mechanisms for review of new genetic tests that minimize both the time and cost of review. These mechanisms should, for example, include the use of deemed reviewers and standards developed in concert with professional organizations. The FDA should give particular attention to the review of genetic tests for predictive purposes and conditions for which a safe and effective intervention has not been established." The draft also recommends that increased knowledge of the clinical validity and utility of genetic tests needs to be generated and that the CLIA regulations should be revised to provide more specific provisions for ensuring the quality of laboratories conducting genetic tests. The draft recommendations have been forwarded to the Assistant Secretary for Health and Surgeon General and the Secretary of the DHHS. The SACGT will invite public comment on the draft and at its next meeting, June 5–7, 2000, will review comments received and subsequently develop a final report to be presented to the Assistant Secretary for Health and Surgeon General and the Secretary of the DHHS.

The recommendations of the SACGT complement a recently released draft Notice of Intent (NOI) formulated by the CLIAC. The NOI serves to advise the public that the DHHS will be preparing a Notice of Proposed Rule Making (NPRM) to revise the CLIA regulations applicable to laboratories that perform human genetic testing. The NOI will be published in the Federal Register before a 60-day period for public comment. The NOI describes a series of proposed changes that summarize the deliberations of the CLIAC over the past 3 years.

Included in the proposed changes is the recommendation that the definition of a molecular genetic or cytogenetic test be "an analysis performed on human DNA, RNA, and chromosomes to detect heritable or acquired disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes. Such purposes would include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations." The NOI also contains a recommendation that laboratories performing genetic testing should i) have assurance that documented informed consent was obtained prior to genetic testing, and that the consent addressed whether the patient agreed to allow re-use of the tested specimen for quality control and quality assurance purposes; ii) have policies in place to protect the confidentiality of genetic test results reporting; and iii) have a clinical consultant associated with the laboratory qualified to provide genetic counseling to the laboratory's clients (care providers, patients, individuals). In a related development, during the course of the SACGT meetings, a group of individuals involved in genetic testing and oversight held informal meetings to discuss how to assure that laboratory concerns about the quality of genetic testing are appropriately addressed. This group has now been formalized as the CDC Genetic Forum-Laboratory Workgroup with a mission of serving as an advisory resource to the SACGT and CLIAC in regard to implementation of proposed changes in regulatory oversight of genetic testing. Furthermore, the Laboratory Workgroup will proactively endeavor to bring important genetic testing issues to the attention of the SACGT and CLIAC and serve as a liaison to the FDA. The next meeting of the Laboratory Workgroup is scheduled for June 2, 2000, in Atlanta, Georgia.

The recommendations of the SACGT and CLIAC are occurring at a time of increased public and governmental concern about genetic testing. A recent executive order by President Clinton prohibits all federal departments and agencies from using genetic information in any hiring or promotion action. The President has endorsed the proposed Genetic Nondiscrimination in Health Insurance and Employment Act of 1999, introduced by Senator Daschle and Congresswoman Slaughter, which would extend these protections to the private sector and to individuals purchasing health insurance. The recommendations of the SACGT and CLIAC advocate additional attention and measures in the pre- and post-analytical phases of genetic testing. Outcomes of this may include making the laboratories performing genetic testing responsible for maintaining documentation of informed consent and providing comprehensive genetic counseling services. Identified in the Final Report of the Task Force on Genetic Testing, and further highlighted by the SACGT, was concern about how new genetic tests are introduced into clinical practice, specifically a concern that genetic tests may be introduced before there is adequate knowledge of the test's clinical validity and

utility. The recommendation by the SACGT that the FDA review all new genetic tests relates directly to this concern and portends a paradigm shift in oversight, especially for academically based genetic testing laboratories. Taken together, the proposed changes in regulatory oversight pose new challenges that are resource-intensive. Will academic clinical laboratories, in the current fiscally restrained health care environment, be able to identify the resources that will be needed to implement the proposed changes and continue to serve as wellsprings for new genetic test development? Professional organizations representing genetic testing laboratories have arrived at a critical juncture where they must voice their perspectives to achieve a workable balance that allows continued and timely introduction of new genetic discoveries into clinical practice. The Executive Council of AMP determined that it is essential for AMP to be represented in the CDC Genetic Forum-Laboratory Workgroup and is planning to participate in the June 2 and subsequent meetings. Concurrently, the Clinical Practice Committee of AMP has begun efforts to develop formal responses to the SACGT draft recommendations and the CLIAC-formulated NOI.

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Editor's note: Dr. Voelkerding, President-Elect of the Association for Molecular Pathology, has coordinated AMP's response to the SACGT request for information, and will serve as the AMP's representative to the CDC Genetic Forum-Laboratory Workgroup.